

**APPARATUS AND METHOD FOR DIAGNOSIS OF  
OPTICALLY IDENTIFIABLE OPHTHALMIC CONDITIONS**

[0001]        **Field of the Invention**

[0002]        The invention relates to testing for physiological and neurological conditions in general and particularly to systems and methods that employ optical imaging of an eye and the responses of individuals to visual stimuli.

[0003]        **Background of the Invention**

[0004]        Numerous systems and methods are known for examining states of health of eyes. For example, U.S. Patent No. 5,065,767, issued November 19, 1991 to Maddess, discloses a psychophysical method for diagnosing glaucoma that employs a time varying contrast pattern. Glaucoma may be indicated for an individual who displays a higher than normal contrast threshold for observing the pattern. Maddess also discloses other tests for glaucoma such as the well-known observation of a scotoma, measurement of intraocular pressure, and assessment of color vision defects. U.S. Patent No. 5,295,495, issued March 24, 1994 to Maddess, discloses systems and methods for diagnosing glaucoma using an individual's response to horizontally moving stripe patterns, which is known as optokinetic nystagmus (OKN). The spatially varying patterns may also vary temporally. In U.S. Patent No. 5,539,482, issued July 23, 1996 to James et al., additional systems and methods for diagnosing glaucoma using spatial as well as temporal variations in contrast patterns are disclosed. U.S. Patent No. 5,912,723, issued June 15, 1999 to Maddess, discloses systems and methods that use a plurality of spatially and temporally varying contrast patterns to improve the methods disclosed in the earlier patents. U.S. Patent No. 6,315,414, issued

November 13, 2001 to Maddess et al., describes systems and methods for making a binocular assessment of possible damage to the optical nerve, optical radiations and white matter of the visual brain indicative of various neurological disorders by measuring responses to visual stimuli.

[0005] U.S. Patent No. 6,068,377, issued May 30, 2000 to McKinnon et al., describes systems and methods for testing for glaucoma using a frequency doubling phenomenon produced by isoluminant color visual stimuli. The disclosure is similar to that of Maddess and co-workers, but uses different, preferably complementary, frequencies of light having the same luminosity as the visual probe signal.

[0006] U.S. Patent Nos. 5,713,353 and 6,113,537 describe systems and methods for testing for blood glucose level using light patterns that vary in intensity, color, rate of flicker, spatial contrast, detail content and or speed. The approach described involves measuring the response of a person to one or more light pattern variations and deducing a blood glucose level by comparing the data to calibration data.

[0007] Other disease conditions and their identification are described in a paper by S. Sokol, entitled "The visually evoked cortical potential in the optic nerve and visual pathway disorders," which was published in *Electrophysiological testing in diseases of the retina, optic nerve, and visual pathway*, edited by G. A. Fishman, published by the American Academy of Ophthalmology, of San Francisco, in 1990, Volume 2, Pages 105-141. An article by Clark Tsai, entitled "Optic Nerve Head and Nerve Fiber Layer in Alzheimer's Disease," which was published in Arch. of Ophthalmology, Vol. 107, February, 1991, states that large diameter neurons are damaged in Alzheimer's disease.

[0008] U.S. Patent No. 5,474,081, issued December 12, 1995 to Livingstone et al.,

describes systems and methods for determining magnocellular defect and dyslexia by presenting temporally and spatially varying patterns, and detecting visually evoked potentials (VEP) using an electrode assembly in contact with the subject being tested.

[0009] U.S. Patent No. 6,129,682, issued October 10, 2000 to Borchert et al., discloses systems and methods for non-invasively measuring intracranial pressure from measurements of an eye, using an imaging scan of the retina of an eye and a measurement of intraocular pressure. The intraocular pressure is measured by standard ocular tonometry, which is a procedure that generally involves contact with the eye. U.S. Patent Nos. 5,830,139, 6,120,460, 6,123,668, 6,123,943, 6,312,393 and 6,423,001 describe various systems and methods that involve mechanical contact with an eye in order to perform various tests. Direct physical contact with an eye involves potential discomfort and risk of injury through inadvertent application of force or transfer of harmful chemical or biological material to the eye. Direct physical contact with an eye is also potentially threatening to some patients, especially those who are young or who may not fully understand the test that is being performed.

[00010] First Generation FDT Instrument

[00011] The Frequency Doubling Technique (hereinafter "FDT") presents back-lit flashed images viewed on a fixed, flat shielded screen in front of a stationary subject. The FDT instrument is similar, but smaller, and the FDT test is substantially shorter in testing duration, as compared to a visual field instrument that tests peripheral and central vision. Visual field testing is standard in all offices providing comprehensive eye exams and treatment of eye disease. The FDT instrument uses sinusoidal grating targets of low spatial frequency (as opposed to simple dots of light in a traditional visual field test). The sinusoidal

gratings are reversed (black to white, and white to black) at 25 Hz. The subject perceives the targets as small striped areas in either central or peripheral vision. As with traditional visual field testing, subjects are seated and have the chin and forehead positioned in a stabilizing rest support. Generally, subjects are tested monocularly. They fixate a target directly in front of them and respond by pushing a button each time they see an image flashed anywhere in their visual field. The instrument records and retests areas based on the subject's responses. A computer program operating on a processor calculates reliability based on fixation losses. The entire test takes less than two minutes per eye. The FDT does not require dilation of the subject's eyes. Therefore, it does not impair vision or the ability to function after the test is performed. The test causes no discomfort. The FDT has received approval from the Federal Drug Administration and has been in clinical use for over four years.

[00012]        There is a need for systems and methods that will provide better information about a larger number of possible conditions using a single testing period, and that will disclose the initial levels of impairment at accuracies that are not presently attainable, while avoiding to the extent possible mechanical contact with the test subject, especially contact with the eye. There is also a need for systems and methods that can be used by non-specialist medical practitioners to screen and evaluate patients without the necessity to first involve a specialist practitioner.

[00013]        **Summary of the Invention**

[00014]        The invention uses more than one observation selected from imaging methods and responses (e.g., a "data set") of a person to provide an assessment of a state of health or medical condition of the person. The images are obtained from any imaging method that

provides image information about a portion of an eye. The responses or data sets are obtained as the response of a person to a test that elicits voluntary or involuntary responses that provide information about a neurological state or condition of the person. The invention combines or correlates information from the more than one observation to provide the assessment.

[00015] In one aspect, the invention relates to an apparatus for performing multiple procedures involving the eye. The apparatus comprises at least one imager for imaging at least a portion of an eye of a patient, the at least one imager configured to provide image data comprises at least two data types selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence topography data, thermal image data, spectroscopic image data, refractometry data, and visible image data and a data analysis module that interrelates data from the at least two data types to provide a interpretive result.

[00016] In one embodiment, the apparatus further comprises a display module that provides a display of analyzed data to a user. In one embodiment, the apparatus further comprises a display module that provides a display of analyzed data to a user using a false color representation for the displayed data.

[00017] In some embodiments, the apparatus further comprises a data output module that reports the interrelated data from the at least two data types. In some embodiments, the apparatus further comprises a report module that reports the interpretive result. In some embodiments, the apparatus further comprises a single output module that reports the interrelated data from the at least two data types and the interpretive result. In some embodiments, the apparatus further comprises a superposition module for superimposing data

obtained from at least two images.

[00018] In some embodiments, the superposition module comprises a module that identifies a fiduciary point in each image to be superimposed, each the fiduciary point representing substantially the same point in the eye; a module that, as necessary, orients an image to be superimposed about the fiduciary point so that a first metric and a second metric are oriented in selected orientations; a module that, as necessary, scales an image so that a first unit of measure associated with the first metric and a second unit of measure associated with the second metric are substantially equal to selected first and second values in each image to be superimposed; and a module that creates a one-to-one correspondence between the fiduciary point, the first metric and the second metric in a first image to be superimposed with the fiduciary point, the first metric and the second metric in a second image to be superimposed.

[00019] In some embodiments, the first metric is a first axial direction, the second metric is a second axial direction that is coplanar with but not parallel to the first axial direction, the first unit of measure associated with the first metric is a length along the first axial direction, and the second unit of measure associated with the second metric is a length along the second axial direction. In some embodiments, the first metric is a first axial direction, the second metric is an angular displacement from the first axial direction, the first unit of measure associated with the first metric is a length along the first axial direction, and the second unit of measure associated with the second metric is a unit of angular measure. In some embodiments, the superposition module comprises a module that identifies a first fiduciary point in each image to be superimposed, each of the first fiduciary points representing substantially the same point in the eye; a module that identifies a second

fiduciary point in each image to be superimposed, each of the second fiduciary points representing substantially the same point in the eye; a module that, as necessary, scales an image so that a distance between the first fiduciary point and the second fiduciary point in the image is substantially equal to a distance between the first fiduciary point and the second fiduciary point in another of the at least two images to be superimposed; and a module that creates a one-to-one correspondence between the first and second fiduciary points of the first image and the second image of the at least two images to be superimposed.

[00020] In some embodiments, the apparatus further comprises a display for displaying the superimposed data obtained from at least two images. In some embodiments, the superimposed data obtained from at least two images comprises data obtained from at least two different data types selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence topography data, thermal image data, spectroscopic image data, and visible image data. In some embodiments, the apparatus further comprises a memory for storing image data. In some embodiments, the memory for storing image data is configured to store and to selectively retrieve data from at least one image for determining changes induced in response to an applied stress. In some embodiments, the applied stress is selected from the group consisting of intra ocular pressure variation, blood pressure variation, oxygen concentration variation, exercise, flashing light, drug administration, administration of insulin, and administration of glucose. In some embodiments, the memory is configured to store and to selectively retrieve data from at least one image for determining a time evolution of changes induced in response to an applied stress. In some embodiments, the memory for storing image data is configured to selectively retrieve data from at least one image for trending analysis purposes. In some embodiments,

the memory for storing image data is configured to archivally store image data.

[00021] In some embodiments, the apparatus further comprises means for aligning the image of the eye of a patient. In some embodiments, the alignment means operates automatically based on the movement of the eye of a patient relative to the imaging means. In some embodiments, the alignment means includes a fixation pattern for focusing a macula of the eye thereon.

[00022] In some embodiments, the data analysis module is configured to automatically determine a presence of an abnormality. In some embodiments, the data analysis module is configured to automatically determine an extent of the abnormality. In some embodiments, the data analysis module comprises a scaling module for providing a scaled estimation of the extent of the abnormality. In some embodiments, the data analysis module is configured to automatically determine a change in the extent of the abnormality over time.

[00023] In some embodiments, the apparatus further comprises an information input module for inputting other patent-related information including at least one from the group of tonometer intraocular pressure, patient-history, family history, blood pressure, vital signs, medication and pupillometry.

[00024] In another aspect the invention feature an apparatus for performing multiple procedures involving the eye. The apparatus comprises a data collection apparatus for collecting a data set corresponding to at least a portion of an eye of a patient, the data collection apparatus configured to provide data indicative of at least two neurological disorders selected from the group consisting of glaucoma, macular degeneration, diabetic retinopathy, Parkinson's disease, Alzheimer's disease, dyslexia, multiple sclerosis, optic neuritis, LDS, head trauma, diabetes, and inappropriate responses to contrast sensitivity



patterns; and a data analysis module that interrelates the data indicative of at least two neurological disorders to provide a interpretive result.

[00025] In some embodiments, the apparatus further comprises a map generation module for generating a map indicative of the presence of a selected one of glaucoma, macular degeneration, and inappropriate responses to contrast sensitivity patterns. In some embodiments, the apparatus further comprises a measurement module for measuring a loss or an apparent loss of ganglion cells associated with a selected one of diabetic retinopathy, Parkinson's disease, and Alzheimer's disease. In some embodiments, the apparatus further comprises a data generating module for generating data indicative of the presence of a selected on of dyslexia, multiple sclerosis, and optic neuritis. In some embodiments, the apparatus further comprises a data output module that reports the interrelated data from the data set. In some embodiments, the apparatus further comprises a report module that reports the interpretive result. In some embodiments, the apparatus further comprises a single output module that reports the interrelated data from the data set and the interpretive result.

[00026] In some embodiments, the apparatus further comprises a superposition module for superimposing data obtained from at least two data sets. In some embodiments, the superposition module comprises a module that identifies a fiduciary point in each data set to be superimposed, each the fiduciary point representing substantially the same point in the eye; a module that, as necessary, orients data to be superimposed about the fiduciary point so that a first metric and a second metric are oriented in selected orientations; a module that, as necessary, scales a data set so that a first unit of measure associated with the first metric and a second unit of measure associated with the second metric are substantially equal to selected first and second values in each data set to be superimposed; and a module that creates a one-

to-one correspondence between the fiduciary point, the first metric and the second metric in a first data set to be superimposed with the fiduciary point, the first metric and the second metric in a second data set to be superimposed. In some embodiments, the first metric is a first axial direction, the second metric is a second axial direction that is coplanar with but not parallel to the first axial direction, the first unit of measure associated with the first metric is a length along the first axial direction, and the second unit of measure associated with the second metric is a length along the second axial direction. In some embodiments, the first metric is a first axial direction, the second metric is an angular displacement from the first axial direction, the first unit of measure associated with the first metric is a length along the first axial direction, and the second unit of measure associated with the second metric is a unit of angular measure.

[00027] In some embodiments, the superposition module comprises a module that identifies a first fiduciary point in each data set to be superimposed, each the first fiduciary point representing substantially the same point in the eye; a module that identifies a second fiduciary point in each data set to be superimposed, each the second fiduciary point representing substantially the same point in the eye; a module that, as necessary, scales a data set so that a distance between the first fiduciary point and the second fiduciary point in the data set is substantially equal to a distance between the first fiduciary point and the second fiduciary point in another of the at least two data sets to be superimposed; and a module that creates a one-to-one correspondence between the first and second fiduciary points of the first data set and the second data set of the at least two data sets to be superimposed. In some embodiments, the apparatus further comprises a display for displaying the superimposed data obtained from at least two data sets.

[00028] In some embodiments, the superimposed data obtained from at least two data sets comprises image data indicative of at least one neurological disorder selected from the group consisting of glaucoma, macular degeneration, diabetic retinopathy, Parkinson's disease, Alzheimer's disease, dyslexia, multiple sclerosis, optic neuritis, LDS, head trauma, diabetes, and inappropriate responses to contrast sensitivity patterns.

[00029] In some embodiments, the apparatus further comprises a memory for storing data. In some embodiments, the memory for storing data is configured to store and to selectively retrieve data from at least one data set for determining changes induced in response to an applied stress. In some embodiments, the applied stress is selected from the group consisting of intra ocular pressure variation, blood pressure variation, oxygen concentration variation, exercise, flashing light, drug administration, administration of insulin, and administration of glucose. In some embodiments, the memory is configured to store and to selectively retrieve data from at least one data set for determining a time evolution of changes induced in response to an applied stress. In some embodiments, the memory for storing data is configured to selectively retrieve data from at least one data set for trending analysis purposes. In some embodiments, the memory for storing data is configured to archivally store data.

[00030] In some embodiments, the apparatus further comprises means for aligning an eye of a patient. In some embodiments, the alignment means operates automatically based on the movement of the eye of a patient relative to the data collection means. In some embodiments, the alignment means includes a fixation pattern for focusing a macula of the eye thereon.

[00031] In some embodiments, the apparatus further comprises means for performing

at least one objective eye-related interpretive procedure relating to a neurological disorder. In some embodiments, the at least one objective eye-related interpretive procedure includes at least one of PERG, OKN and VEP. In one embodiment, the apparatus further comprises a display module that provides a display of analyzed data to a user. In one embodiment, the apparatus further comprises a display module that provides a display of analyzed data to a user using a false color representation for the displayed data.

[00032] In some embodiments, the data analysis module is configured to automatically determine a presence of an abnormality. In some embodiments, the data analysis module is configured to automatically determine an extent of the abnormality. In some embodiments, the data analysis module comprises a scaling module for providing a scaled estimation of the extent of the abnormality. In some embodiments, the data analysis module is configured to automatically determine a change in the extent of the abnormality over time.

[00033] In some embodiments, the apparatus further comprises an information input module for inputting other patient-related information including at least one from the group of tonometer intraocular pressure, patient-history, family history, blood pressure, vital signs, medication and pupillometry.

[00034] In a further aspect the invention features an apparatus for performing multiple procedures involving the eye. The apparatus comprises an imager for imaging at least a portion of an eye of a patient, the imager configured to provide image data; a data collection apparatus for collecting a data set corresponding to at least a portion of an eye of a patient, the data collection apparatus configured to provide data indicative of a neurological disorders; and a data analysis module that interrelates the image data and the data indicative of a neurological disorder to provide a interpretive result.

[00035] In one embodiment, the image data comprises a data type selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence topography data, thermal image data, spectroscopic image data, refractometry data, and visible image data. In one embodiment, the neurological disorder is selected from the group consisting of glaucoma, macular degeneration, diabetic retinopathy, Parkinson's disease, Alzheimer's disease, dyslexia, multiple sclerosis, optic neuritis, LDS, head trauma, diabetes, and inappropriate responses to contrast sensitivity patterns.

[00036] In some embodiments, the apparatus further comprises a data output module that reports the interrelated data from the image data and the data indicative of a neurological disorder.

[00037] In some embodiments, the apparatus further comprises a report module that reports the interpretive result. In some embodiments, the apparatus further comprises a single output module that reports the interrelated data from the image data and the data indicative of a neurological disorder and the interpretive result. In one embodiment, the apparatus further comprises a display module that provides a display of analyzed data to a user. In one embodiment, the apparatus further comprises a display module that provides a display of analyzed data to a user using a false color representation for the displayed data.

[00038] In some embodiments, the apparatus further comprises a superposition module for superimposing data obtained from an image and data indicative of a neurological disorder. In some embodiments, the superposition module comprises a module that identifies a fiduciary point in the image to be superimposed, and a fiduciary point in the data indicative of a neurological disorder, each the fiduciary point representing substantially the same point

in the eye; a module that, as necessary, orients at least one of the image and the data indicative of a neurological disorder to be superimposed about the fiduciary point so that a first metric and a second metric are oriented in selected orientations; a module that, as necessary, scales at least one of the image and the data indicative of a neurological disorder so that a first unit of measure associated with the first metric and a second unit of measure associated with the second metric are substantially equal to selected first and second values in each of the image and the data indicative of a neurological disorder to be superimposed; and a module that creates a one-to-one correspondence between the fiduciary point, the first metric and the second metric in the image to be superimposed with the fiduciary point, the first metric and the second metric in the data indicative of a neurological disorder to be superimposed. In some embodiments, the first metric is a first axial direction, the second metric is a second axial direction that is coplanar with but not parallel to the first axial direction, the first unit of measure associated with the first metric is a length along the first axial direction, and the second unit of measure associated with the second metric is a length along the second axial direction. In some embodiments, the first metric is a first axial direction, the second metric is an angular displacement from the first axial direction, the first unit of measure associated with the first metric is a length along the first axial direction, and the second unit of measure associated with the second metric is a unit of angular measure. In some embodiments, the superposition module comprises a module that identifies a first fiduciary point in each of the image and the data indicative of a neurological disorder to be superimposed, each the first fiduciary point representing substantially the same point in the eye; a module that identifies a second fiduciary point in each of the image and the data indicative of a neurological disorder to be superimposed, each the second fiduciary point

representing substantially the same point in the eye; a module that, as necessary, scales an image so that a distance between the first fiduciary point and the second fiduciary point in the image is substantially equal to a distance between the first fiduciary point and the second fiduciary point in the data indicative of a neurological disorder to be superimposed; and a module that creates a one-to-one correspondence between the first and second fiduciary points of the image and the data indicative of a neurological disorder to be superimposed.

[00039] In some embodiments, the apparatus further comprises a display for displaying the superimposed data obtained from the image and the data indicative of a neurological disorder. In some embodiments, the apparatus further comprises a memory for storing data, the data comprises at least one of image data and data indicative of a neurological disorder. In some embodiments, the memory for storing data is configured to store and to selectively retrieve data for determining changes induced in response to an applied stress. In some embodiments, the applied stress is selected from the group consisting of intra ocular pressure variation, blood pressure variation, oxygen concentration variation, exercise, flashing light, drug administration, administration of insulin, and administration of glucose. In some embodiments, the memory is configured to store and to selectively retrieve data for determining a time evolution of changes induced in response to an applied stress. In some embodiments, the memory for storing data is configured to selectively retrieve data for trending analysis purposes. In some embodiments, the memory for storing data is configured to archivally store data.

[00040] In some embodiments, the apparatus further comprises means for aligning the image of the eye of a patient. In some embodiments, the alignment means operates automatically based on the movement of the eye of a patient relative to the imaging means.

In some embodiments, the alignment means includes a fixation pattern for focusing a macula of the eye thereon.

[00041] In some embodiments, the apparatus further comprises means for performing at least one objective eye-related interpretive procedure. In some embodiments, the at least one objective eye-related interpretive procedure includes at least one of PERG, OKN and VEP. In one embodiment, the apparatus further comprises a display module that provides a display of analyzed data to a user. In one embodiment, the apparatus further comprises a display module that provides a display of analyzed data to a user using a false color representation for the displayed data.

[00042] In some embodiments, the data analysis module is configured to automatically determine a presence of an abnormality. In some embodiments, the data analysis module is configured to automatically determine an extent of the abnormality. In some embodiments, the data analysis module comprises a scaling module for providing a scaled estimation of the extent of the abnormality. In some embodiments, the data analysis module is configured to automatically determine a change in the extent of the abnormality over time.

[00043] In some embodiments, the apparatus further comprises an information input module for inputting other patient-related information including at least one from the group of tonometer intraocular pressure, patient-history, family history, blood pressure, vital signs, medication and pupillometry.

[00044] In yet a further aspect, the invention relates to a method of treating a patient. The method comprises the steps of performing an examination of a patient using the apparatus described in any of the first three aspects of the invention and treating the patient based at least in part on a result obtained from the examination. In some embodiments, the



method of treatment further comprises the step of providing the treatment based at least in part on information stored in a memory.

[00045] In a further aspect, the invention features a computer program recorded on a machine-readable medium. The computer program comprises a data analysis module that interrelates at least two data types, the at least two data types selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence topography data, thermal image data, spectroscopic image data, refractometry data, and visible image data.

[00046] In a still further aspect the invention relates to a computer program recorded on a machine-readable medium. The computer program comprises a data analysis module that interrelates at least two types of data indicative of a neurological disorder selected from the group consisting of inappropriate responses to contrast sensitivity patterns, glaucoma, macular degeneration, diabetic retinopathy, Parkinson's disease, Alzheimer's disease, dyslexia, multiple sclerosis, and optic neuritis.

[00047] In yet a further aspect the invention features a computer program recorded on a machine-readable medium. The computer program comprises a data analysis module that interrelates image data and data indicative of a neurological disorder, the image data comprises a data type selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence topography data, thermal image data, spectroscopic image data, refractometry data, and visible image data, and the data indicative of a neurological disorder selected from the group consisting of glaucoma, macular degeneration, diabetic retinopathy, Parkinson's disease, Alzheimer's disease, dyslexia, multiple sclerosis, optic neuritis, LDS, head trauma, diabetes, and inappropriate

responses to contrast sensitivity patterns.

[00048] In a further aspect, the invention relates to a method of diagnosis of a state of health of a patient. The method comprises the steps of imaging at least a portion of an eye of a patient to obtain image data comprises at least two data types selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence topography data, thermal image data, spectroscopic image data, refractometry data, and visible image data; and interrelating the data from the at least two data types to provide a interpretive result.

[00049] In another aspect, the invention features a method of diagnosis of a state of health of a patient. The method comprises the steps of imaging at least a portion of an eye of a patient to obtain image data indicative of at least two neurological disorders selected from the group consisting of glaucoma, macular degeneration, diabetic retinopathy, Parkinson's disease, Alzheimer's disease, dyslexia, multiple sclerosis, optic neuritis, LDS, head trauma, diabetes, and inappropriate responses to contrast sensitivity patterns; and interrelating the image data indicative of the at least two neurological disorders to provide a interpretive result.

[00050] In still another aspect, the invention relates to a method of diagnosis of a state of health of a patient. The method comprises the steps of imaging at least a portion of an eye of a patient to obtain image data comprises a data type selected from the group consisting of data from ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence topography data, thermal image data, spectroscopic image data, refractometry data, and visible image data, and data indicative of a neurological disorder selected from the group consisting of glaucoma, macular degeneration, diabetic retinopathy,

Parkinson's disease, Alzheimer's disease, dyslexia, multiple sclerosis, optic neuritis, LDS, head trauma, diabetes, and inappropriate responses to contrast sensitivity patterns; and interrelating the image data and the data indicative of a neurological disorder to provide a interpretive result.

[00051]        The foregoing and other objects, aspects, features, and advantages of the invention will become more apparent from the following description and from the claims.

[00052]        **Brief Description of the Drawings**

[00053]        The objects and features of the invention can be better understood with reference to the drawings described below, and the claims. The drawings are not necessarily to scale, emphasis instead generally being placed upon illustrating the principles of the invention. In the drawings, like numerals are used to indicate like parts throughout the various views.

[00054]        Fig. 1A is a prior art diagram showing some of the physiology of the eye and the brain in humans;

[00055]        Fig. 1B depicts a prior art cross sectional diagram showing a feedback loop from the visual cortex to the LGN;

[00056]        Fig. 2 is a schematic representation of an exemplary apparatus suitable for use according to the invention;

[00057]        Fig. 3A shows a schematic diagram of the disposition of an eye monitoring device relative to an eye of a person being tested according to the invention;

[00058]        Fig. 3B shows a diagram that depicts the interrelationship among the features of an eye of a person being tested, and the areas of the eye sensed by two sensors, according

to the invention;

[00059] Fig. 3C shows a diagram that depicts the interrelationship between the features of an eye of a person being tested, and the areas of the eye sensed by one sensor, according to the invention;

[00060] Fig. 3D shows a diagram that depicts a test pattern and a fixation signal that is useful for fixating an eye of a person being tested when one sensor is employed in the eye monitoring device, according to the invention;

[00061] Fig. 4 is a flow chart showing the steps in the operation of the instrument of the invention, or alternatively, showing the interrelationships among the modules comprising apparatus according to the invention;

[00062] Fig. 5 is a diagram that shows components of a superposition module according to the invention;

[00063] Fig. 6 is a diagram showing a region of frequency space having both temporal and spatial frequency variations, and indicating a typical person's reaction thereto, as is known in the prior art;

[00064] Figs. 7A and 7 B are drawings that depict a display space that is segmented and includes an illustrative contrast pattern, as is known in the prior art;

[00065] Figs. 8 A, 8B and 8C are diagrams that show the relationship between an image and a data set, two images taken at different times, and a series of images, false color data representations, and data sets, respectively, according to principles of the invention;

[00066] Fig. 9 is a schematic showing the relationship among superimposed images and/or data sets, according to principles of the invention; and

[00067] Fig. 10 shows a hand-held apparatus that measures a person's visual contrast

sensitivity according to principles of the invention.

[00068]        **Detailed Description of the Invention**

[00069]        The invention provides systems and methods for determining a wide range of possible medical conditions, including normal health, the early (or onset) stage of a disease condition, and the development of the disease condition up to a fully presented disease conditions (e.g., diagnosis, staging, and monitoring). The invention provides the ability to diagnose the severity of various disease conditions. By application of the methods of the invention over time, one can monitor the rate and extent of evolution of various disease conditions in a particular individual.

[00070]        The invention uses a combination of two or more observations, which can include an image of at least a portion of an eye of a patient, and a data set corresponding to a response from at least a portion of an eye of a patient. The two or more observations can comprise two images, an image and a data set, or two data sets. Images and data sets will be referred to generally as information, which should be understood as necessary to mean either images or data sets or both. The images include visualization of a portion of an eye, and can include ophthalmic images using confocal microscopy data, retinal polarimetry data, optical coherence topography data, thermal image data, spectroscopic image data, refractometry data, and visible image data. The data sets include data that is indicative of neurological disorders. For example, the neurological disorders include glaucoma, macular degeneration, diabetic retinopathy, Parkinson's disease, Alzheimer's disease, dyslexia, multiple sclerosis, optic neuritis, and inappropriate responses to contrast sensitivity patterns. In some embodiments, the images are visible images that include color fundus photography and black and white

fluorescein angiography.

[00071] The functional deficits of glaucoma and Alzheimer's Disease (hereinafter "AD") include loss in low spatial frequency ranges in contrast sensitivity, and are similar in both diseases. Glaucoma, unlike AD, involves losses of optic nerve fiber layer originating in the retina. At present, the only definitive diagnosis of AD involves identifying amyloid plaques and neuro-fibrillary tangles in the neurons of the cortex by microscopic analysis of brain tissue. The invasive nature of the test necessitates that the test be performed after death. A test specific for low spatial frequency deficits, as is available for diagnosing glaucoma, would be useful in measuring similar deficits in AD. The Frequency Doubling Technique (hereinafter "FDT"), unlike many other tests of visual function, does not require a high degree of concentration or of cognition. Because FDT takes only two minutes to administer to both eyes, it is appropriate for subjects who have difficulty concentrating for long periods.

[00072] Visual Deficits and Cognitive Function

[00073] Visual dysfunction appears to be a strong predictor of cognitive dysfunction in subjects with AD. Pattern masking has been found to be a good predictor of cognitive performance in numerous standard cognitive tests. The tests found to correlate with pattern masking included Gollin, Stroop-Work, WAIS-PA, Stroop-Color, Geo-Complex Copy, Stroop-Mixed and RCPM. Losses in contrast sensitivity at the lowest spatial frequency also was predictive of cognitive losses in the seven tests. AD subjects have abnormal word reading thresholds corresponding to their severity of cognitive impairment and reduced contrast sensitivity in all spatial frequencies as compared to normal subjects.

[00074] Review of the Physiology of Vision

[00075] The visual system is believed to be made up of two parallel pathways: the M

pathway and the P pathway. The pathways have individualized function. There are a total of approximately 160 million rod and cone cells in the normal eye. There are approximately 1.2 million ganglion cells (M and P cells) in the normal eye. The magnocellular or M pathway (comprising M cells) is sensitive to contrast sensitivity and motion. M cells comprise both My cells (usually associated with contrast sensitivity) and Mx cells (usually associated with motion). There are estimated to be approximately 12,000 cells of the My type in the normal eye. The magnocellular M system has high contrast gain and saturates at relatively low contrasts. The parvocellular or P pathway (comprising P cells) is specialized for processing color and form. The parvocellular P system has a low contrast gain and more linear contrast visual stimuli. Losses specific to the M pathway have been identified in subjects with AD even in brain areas devoid of plaques and neurofibrillary tangles. The M pathway shows signs of significant cell loss in AD subjects. In studies of primates, lesions have been found in the magnocellular layers of the lateral geniculate nucleus that does not impact contrast sensitivity for stationary gratings. However, such lesions do impact sensitivity for events involving motion or high temporal content. It has been found in primates that lesions identified in the parvocellular layers of the lateral geniculate nucleus (LGN) impacted contrast sensitivity for stationary or low temporal content events.

[00076]        Review of the Pathology of Glaucoma

[00077]        Glaucoma is a disease that is categorized by increasing internal eye pressure on the optic nerve. The compression of the nerve causes nerve fiber morbidity and eventually cell loss. It is believed that the M ganglion cells of the visual system are impacted to a greater extent than the P cells in glaucoma. M cells are fewer in number, have larger axon diameter and larger receptive fields. Measurements of the visual field, measurements of

intraocular pressure and observation of changes in the nerve fiber layer and optic disc are utilized to diagnosis and manage glaucoma. In glaucoma, the location of optic nerve change and pallor corresponds to location and density of visual field loss. New technologies that detect image losses in the nerve fiber layer may have the ability to detect glaucoma damage prior to the appearance of measurable visual field losses.

[00078] Contrast sensitivity function is frequently reduced in glaucoma. There is a high correlation of low spatial frequency contrast sensitivity loss and the mean visual field loss in glaucoma. Higher rates of glaucoma have been found among patients with AD compared to a control group. The diagnosis of glaucoma was based on the visual field defects or optic nerve cupping. Higher rates of glaucoma have also been found among patient's diagnosed with Parkinson's disease.

[00079] Visual field loss is a definitive sign of glaucoma and loss in visual field correlates with loss in contrast sensitivity. The appearance of optic nerve fiber loss detected either by observation of the fundus of the eye or by the application of newer technologies also correlates with visual field losses. The technology of the present invention may detect losses in visual field at earlier stages than the traditional instrumentation of visual field loss can measure the losses. The conclusion that optic nerve appearance and loss in the nerve fiber layer would correlate with loss in contrast sensitivity is a reasonable one in the case of glaucoma. Other diseases that have losses in contrast sensitivity also have losses in the nerve fiber layer and changes in optic nerve appearance.

[00080] Frequency Doubling Technology and Glaucoma

[00081] FDT has been shown to detect glaucomatous changes at earlier stages than are detected with stereophotographs, and has better sensitivity and specificity than motion-



automated perimetry. FDT is a better predictor of progressive field loss as measured by standard automated perimetry than pattern electroretinography in a population of chronic open angle glaucoma. FDT is useful for detection of early glaucomatous visual field damage as compared to a Humphrey Field Analyzer and a high pass resolution perimeter.

[00082] In the FDT instrument, the sinusoidal gratings are reversed (black to white, and white to black) at 25 Hz. This stimulates the My ganglion cells. The contrast between the light and dark lines in the sinusoidal grating targets is changed in order to determine a threshold of perception of the target which is related to the healthy My type ganglion cells of the retina. A standard visual field test stimulates all ganglion cell types. It is believed that the My cells are the first ganglion cells to die in glaucoma. Therefore, FDT provides earlier detection of glaucoma. Subjects with AD have reductions in low spatial frequency, the same function that the FDT tests. The same cells may be impacted by AD compared to glaucoma, but the mechanism of cell death differs.

[00083] Review of the Pathology of AD

[00084] There has long been controversy as to the primary cause of AD visual symptoms. It is well documented that there are contrast sensitivity reductions, in particular at low spatial frequencies, in AD. Abnormal visual perception and abnormal visuospatial processing are common with patients diagnosed as having AD.

[00085] AD is a progressive degenerative disease of the brain leading to senility and dementia. It is known to affect millions of people and the numbers are rapidly growing. There are numerous forms of dementia, AD being only one, albeit the most devastating. Cognitive questionnaires do not accurately separate AD from other forms of dementia.

[00086] Numerous pharmaceutical companies are working on treatments for AD that

will slow the progression and, in some cases, reverse the effects of AD. What is needed is a definitive, non-invasive test for AD prior to death.

[00087] AD is a large diameter neuron disease (Tsai 1991). Some researchers have found microscopic amyloid plaques on retinal ganglion cells, but not in all cases, and not at all stages of the disease. Sadun (1990) found loss in M-type retinal ganglion cells, contrast sensitivity, and visual fields in the absence of plaques or tangles, but other researchers were unable to reproduce these findings, suggesting that there is a progression in the disease with varying symptoms. Most researchers agree that amyloid plaques and tangles on cortical neurons is definitive of AD. Because a longitudinal study on suspect AD patients is impossible due to the invasiveness of the procedure, the progression of AD is not understood in detail.

[00088] Documentation of Retinal Ganglion

[00089] The degeneration in the retinal ganglion cells (RGC) of patients with Alzheimer's Disease was identified using histopathologic measure. Sadun found degeneration of the retinal ganglion cells and axonal degeneration upon examining the retro bulbar optic nerves. There was a greater frequency of degeneration the more posterior the nerve was located. A possible implication is that the retinal ganglion cell loss may be secondary to retrograde axonal degeneration.

[00090] Nerve Fiber Layer Analysis

[00091] A significant reduction in nerve fiber thickness in AD subjects compared to normal subjects has been observed using OCT Humphreys.

[00092] The present invention provides novel systems and methods for non-invasively diagnosing and tracking AD, based on a new theory of the progression of AD. In one aspect

of the theory, the optic nerves are an extension of the brain and therefore provide a window to the workings of the brain. In one embodiment, the Welch Allyn Frequency Doubled Technology (FDT) visual field exam isolates retinal ganglion cells of the My type. These cells are associated with contrast sensitivity. Due to their large diameter, they are generally, though not universally, believed to be some of the first cells to die in glaucoma. Presumably, the ganglion cells are damaged by an ischemic effect when passing through bent lamina cribrosa as a result of elevated intra-ocular pressure (IOP).

[00093] FDT has become the gold standard for early diagnosis and tracking of glaucoma. Anecdotally, FDT has produced false positive diagnoses of glaucoma, when subsequent analysis indicated diagnoses of tumor, macular degeneration, diabetic retinopathy, multiple sclerosis, and other neurological diseases.

[00094] In addition, various researchers have suggested that glaucomatous damage may extend beyond the retinal ganglion cells into the lateral geniculate nucleus (LGN) and the visual cortex, and that the frequency doubled illusion may be mediated by a cortical loss of temporal phase discrimination, thus again suggesting that neuron involvement is not limited to ganglion cells.

[00095] Fig. 1A is a prior art diagram showing some of the physiology of the eye and the brain in humans. Fig. 1B is a prior art cross sectional diagram showing a feedback loop from the visual cortex to the LGN. In fact, approximately 80% of the axons feeding the LGN come from the visual cortex, while approximately 20% come from the retina.

[00096] Clinical evaluations are currently underway to determine the efficacy of using FDT to diagnose and track AD. One unanswered question is whether FDT should be optimized to increase sensitivity and specificity. Although My cells are likely involved in

AD, other forms of ganglion cells are also likely involved, such as Mx cells and P cells. Thus, the FDT zone shapes and sizes, spatial frequency, and temporal frequency may be optimized to isolate different forms of ganglion cells and their interaction with feedback neurons from the visual cortex. At early stages of the disease, plaques and tangles likely form in the visual cortex, thus sending an abnormal feedback to the LGN. This corticofugal feedback affects the signals from the retina leading through the LGN to the visual cortex. The result is an abnormal FDT finding. This effect may or may not be associated with ganglion cell damage caused by atrophy at a given stage in the disease. The exact etiology will only be known for certain after cross-sectional and longitudinal clinical evaluations are performed with subsequent histological analysis of the neurons. The mechanism for ganglion cells loss will likely differ from glaucoma in that there need not be elevated IOP in AD.

[00097] Similarly, it is believed that other neurological disorders (such as macular degeneration, diabetic retinopathy, optic neuritis, papilledema, anterior ischemic optic neuropathy, and tumor) can be diagnosed and tracked by optimizing FDT (A Primer for Frequency Doubling Technology, Johnson, 1998). AD and Parkinson's were not mentioned in this product literature and are the subject of this treatise and latest invention. An improved FDT technology, hereinafter FDT2, may be a better, though slower, test for AD in that there are significantly smaller interrogated areas than in the original FDT, thus leading to detection of loss at an earlier stage and more accurate tracking of AD. FDT2 can achieve resolution that is impossible with FDT, thereby providing results that could not have been provided heretofore.

[00098] It is believed that at some point before the disease process has advanced to the stage where AD can be diagnosed using present day methods, functional vision losses

associated with AD becomes apparent in the optic nerve, nerve fiber layer and retina. In one embodiment, the retina includes the peripheral retina. A variety of nerve fiber imaging techniques and photographic techniques have demonstrated changes in the optic nerve of subjects with AD. However, subjective testing relying on visual fields and perimetry techniques prove unreliable in AD subjects because of poor attentive skills. The FDT2 is a modified visual field test of short duration. Additionally, low spatial frequency targets are used to sample test areas. This FDT2 instrument has the ability to measure field losses in AD subjects as well as localize retinal areas exhibiting low spatial frequency deficits.

[00099] Studies of the visual symptoms of AD findings observed in brain lesions have shown that damage occurs in the visual association cortex and other cortical areas, as well as the primary visual cortex.

[000100] It is believed that at some point other than early in the disease process, losses associated with AD become apparent in the optic nerve and nerve fiber layer. Because it is a low spatial frequency test, the FDT will pick up such losses unlike other subjective testing such as traditional visual field techniques. The source of degeneration in the visual system does not likely originate at the level of the retinal ganglion cells. However, it seems these tissues are not spared in AD. It has long been demonstrated that pathologies originating in the higher areas of brain function eventually appear as pathology to the optic disc and nerve fiber layer. It has been shown by means of stereo photos that loss in the optic disc and nerve fiber layer are measurable in AD at some stage.

[000101] There is evidence that there are right and left field advantages for some visual functions. Because the FDT is a test of function in many ways similar to a standard visual field, it is possible to test split visual fields and therefore isolate in each eye right retinal

function and left retinal function. It is also possible to compare the function of the right eye to the function of the left eye.

[000102] Histopathology studies of the optic nerve of subjects with AD were thought to show axonal degeneration originating from the retina. There is a loss of both large and small diameter ganglion cell layer neurons. These studies concluded there is a greater drop out of the larger neurons which project to the M layers of the lateral geniculate nucleus. Based on studies of primate retina and visual function, if there is a loss of cells along the M pathway, it would be expected that there would be reductions in the ability to perceive motion or high temporal content events. Several studies of AD subjects have reported this. Indirect comparisons of losses in both the P channels and the M channels showed that the M channel function deteriorates at a greater rate than the P channel function in AD.

[000103] The Present Invention

[000104] It is believed that the optic nerves, as direct and intimate extensions of the brain, are likely to be among the earliest nerves to exhibit changes associated with various neurological disorders. It is believed that these neurological disorders are observable by imaging the eye and measuring changes (or deviations) therein from what is considered normal, as well as in neurological responses that are manifested in the behavior and response of the eye, including the retina and the optic nerves. In addition, objective tests such as OKN, VEP and pattern electroretinograms (PERG) can be implemented in the systems and methods of the invention. Objective tests are useful with infants and geriatrics, as well as those who have difficulty communicating or following specific directions.

[000105] Based on the image and/or data set information that is observed, the invention provides an interpretive result. The term "interpretive result" is defined herein to mean a

diagnosis (or a proposed diagnosis), or a change in physical condition or medical status over time, which a medical practitioner can consult in order to propose a course of treatment for the individual patient in question. It is not to be inferred that the suggested diagnosis or indication of physical condition or medical status is to be taken as medical advice *per se*, but rather should be understood as an aid to a practitioner, who must still apply his or her best medical judgment in counseling the patient.

[000106] Turning to Fig. 2, there is shown a schematic representation of an exemplary apparatus 100 suitable for use according to principles of the invention. The apparatus 100 comprises a core portion 110 that in some embodiments can be portable or hand held. The core portion 110 comprises a processor 112, which in some embodiments is a single board computer (SBC). The SBC is based on a microprocessor, such as an Intel x86 family member or an equivalent processor. The processor 112 communicates with a microcontroller (MCU) 114 by way of a bus 115, which is in one embodiment an RS-232 bus. In some embodiments the MCU 114 is a Motorola MC68332, which is a highly-integrated 32 bit microcontroller that combines high-performance data manipulation capabilities with peripheral subsystems. The Motorola MC68332 comprises a 32 bit CPU, a system integration module, a time processing unit, a queued serial module and a 2 Kbyte static RAM module with time processing unit emulation capability. A memory device 116 is connected bi-directionally with the processor 112. The memory device can be any conventional machine-readable and -writable storage device, including any or all of RAM, DRAM, SDRAM, magnetic memory, and optical memory. The core portion 110 also comprises a port 118, such as a universal serial bus (USB) or wireless port, for attaching external devices, such as a retina camera 134, to the core portion 110. In some embodiments, an optional port

119 is provided for attaching one or more electrodes 135, or other signal acquisition hardware, to the core portion 110.

[000107] The core portion 110 also comprises an eye monitoring device 120 for monitoring an eye of a person being tested or evaluated, including motion of the eye. In Fig. 2, the eye monitoring device 120 is represented by a video camera; however, another embodiment is described hereinbelow, in which a simpler and less expensive device comprising one or more linear charge-coupled device (CCD) arrays is presented. The core portion 110 further comprises a display 122, for displaying information to an operator of the instrument, which display 122 in some embodiments is a liquid crystal display (LCD). Additional portions of the instrument are attached to the core portion 110.

[000108] In some embodiments, the core portion 110 is connected to one or more of operator input devices, which in some embodiments are a keyboard 124, a mouse 126, or other devices such as a microphone (not shown). The operator input devices communicate with the processor 112 by way of any conventional wired or wireless connection. In some embodiments, the core portion 110 is connected to one or more output devices such as a printer 128 or a speaker (not shown) for communicating to a user of for creating a hard copy of a record, such as the observations and assessments that are generated during a test. By use of the operator input and output devices, an operator can introduce, and can record as hard copy, information such as a person's name, other identifying information, and other patent-related information such as tonometer intraocular pressure, patient-history, family history, blood pressure, vital signs, medication, and pupillometry, as well as any test conditions, such as an applied stress. An applied stress can comprise any one of intra ocular pressure variation, blood pressure variation, oxygen concentration variation, exercise, flashing light,



drug administration, administration of insulin, and administration of glucose, or combinations thereof.

[000109] A display 130 is provided for displaying test patterns or other material to a person being tested. The display 130 is connected to the core portion 110 by way of an electrical connector and cable 131 and receives signals from the MCU 114 as input to be displayed. The core portion 110 also has attached thereto a response device 132, such as a mouse or a button that can be manipulated or otherwise activated by a person being tested to communicate responses to the MCU 114 by way of a cable and connector 133. In some embodiments, the display 130 and the response device are a unitary device, such as a touchscreen, and/or the connections with the MCU 114 are made by wireless methods, such as RF or infrared communication links using any conventional wireless technology (for example, 802.11a, 802.11b, or 802.11g).

[000110] The core portion 110 is connected to a retina camera 134 by way of the port 118, for viewing the fundus of an eye. In one embodiment, the retina camera 134 is a device such as the Welch Allyn Model 11820 PanOptic™ Ophthalmoscope, available from Welch Allyn, Skaneateles Falls, NY, with the addition of a video pickup to provide an electrical input signal to the core portion 110 of the apparatus 100.

[000111] In one embodiment, the retinal camera comprises a sensor such as a CCD array that converts detected light into charge signals. The charge signals are in general proportional to an illumination level and a duration of an exposure. The charge signals are converted, on a pixel by pixel basis, into analog signals or digital signals, as may be desired using conventional circuitry, such as switching circuitry, sample and hold circuitry, amplification circuitry, filters, and analog to digital converters. Digital representations of the

images detected can be provided with resolution defined by the capability of an analog to digital converter, ranging today from one bit resolution to 24 bit resolution, and with higher resolution as may become possible in the future. Both gray scale and color can be resolved. Additional detailed description of embodiments of video devices suitable for use according to principles of the invention is presented in U.S. Patent No. US 6,527,390 B2 and U.S. Patent Application Publication No. US 2002/0097379 A1, both of which are assigned to the common assignee of this application, and the entire contents of each of which is hereby incorporated herein by reference.

[000112] In some embodiments, one or more electrodes 135 can be attached to the core portion 110 by way of a port 119. The one or more electrodes 135, or other signal acquisition hardware, are used to acquire electrical signals, for example, electrical potentials generated during testing, such as visually evoked potentials or other electrical signals useful in detecting responses of a person being tested.

[000113] A computer 136, which in various embodiments is a personal computer, a laptop computer, or another general purpose programmable computer of similar or greater capability, is provided for analysis of images and data sets that are collected in the course of testing a person. The images and data sets are communicated from the core portion 110 to the computer 136 by way of any of a wired connection link 140, such as an RS-232 communication bus, a wireless communication link 142, such as RF or infrared, or by transfer using removable media such as a CD-RW disc 138 or a floppy or zip disk 144. In some embodiments, communication from the computer 136 to the core portion 110 is provided by any of the wired link 140, wireless link 142, and transfer using removable media such as CD-RW disc 138 and floppy or zip disk 144, so that commands in the form of

programs, program modules, or individual commands to perform a specific action can be downloaded from the computer 136 to the core portion 110, or can be accessed by the core portion 110 while resident at the computer 136. To this end, each of the computer 136 and the core portion 110 are provided with the appropriate ports and/or read-write devices for reading and writing media as necessary. The core portion 110 and the computer 136, as well as the other attached devices, are powered by conventional line voltage connections using wall plugs and power supplies, or by the use of batteries, as appropriate, depending on the intended use of the apparatus, e.g., in an office setting, or in a field setting.

[000114] Figs. 3A-3D show generally an approach to providing an eye monitoring device 120 useful for monitoring the motion of an eye. Fig. 3A shows a schematic diagram 200 of the disposition of an eye monitoring device 120 relative to an eye 260 of a person being tested. In addition, Fig. 3A indicates at a high level the relative disposition of components within the eye monitoring device 120, which is a hand held, portable device in the embodiment depicted. The eye monitoring device 120 comprises, in one embodiment, a handle 210 that provides a gripping structure for a practitioner to hold and position the eye monitoring device 120 relative to the eye 260. The handle 210 is adapted to contain the battery useful for operating the device and the electronics useful for manipulating data, providing control signals, and communicating commands and data to and from the eye monitoring device 120. A head portion 220 of the eye monitoring device 120 contains a display 230, such as a CRT, for displaying a test pattern to the eye 260. The head portion 220 additionally contains one or more sensors 240 that are aimed to detect light reflected from a surface of the eye 260. The one or more sensors 240 in one embodiment are 1024 x 1 CCD arrays capable of detecting light at each of 1024 pixel locations, and providing an electrical

signal proportional to an intensity of light detected at each pixel. The one or more sensors 240 are focused on a surface of the eye 260 by optics 250, which can be constructed of one or more components made from any convenient optically transmissive material such as glass or plastic.

[000115] Fig. 3B shows a diagram 202 that depicts the interrelationship among the features of an eye 260 of a person being tested, and the areas 242, 244 of the eye sensed by two sensors. The eye 260 is being viewed straight on in Fig. 3B, and features of the eye 260 including the white area 262, the iris 264, and the limbus 266 of the iris 264 are represented. Two areas of focus 242, 244 of two sensors, such as the one or more sensor 240 of Fig. 3A, are depicted on the surface of the eye 260. One area of focus 242 is positioned along an imaginary horizontal line (i.e., line 268 in Fig. 3C) passing through the center of substantially circular limbus 266. A second area of focus 244 is positioned along a second imaginary horizontal line parallel to the first imaginary horizontal line, but above (or alternatively, below) the first area of focus 242 by an offset of dimensions of millimeters. Each of the two sensors (not shown) can detect an intensity of light reflected from different locations on the surface of the eye 260. A white portion 262 of the surface of the eye 260 will in general reflect light more strongly than a darker portion of the surface of the eye 260, such as the iris 264, or the pupil of the eye situated within the iris 264. As the eye moves, the change in intensity of light reflected from the white portion 262 as compared to the intensity of light reflected from the iris 264 is tracked. Position is measured as a pixel location counted from one end of a sensor 240. The position of the change in intensity of reflected light corresponds to the location of the limbus 266. When the two sensors detect a change in the position of the limbus, the direction of motion of the eye can be deduced. By applying standard discrete

time analysis, the velocity of the motion can also be deduced as  $x\text{-axis velocity} = k(DX/DT)$ , where  $k$  is a constant,  $DX$  is a change in position along an  $X$  axis, and  $DT$  is a change in time, and a  $y$ -axis velocity can be determined as  $y\text{ axis velocity} = k(DY/DT)$ , where  $DY$  is a change in position along a  $Y$  axis. As is well known in the mathematical analysis arts, two data inputs that are independent with respect to  $x$ - and  $y$ -axis motion are sufficient to determine both motions and their velocities.

[000116] Fig. 3C shows a diagram 204 that depicts the interrelationship between the features of an eye 260 of a person being tested, and the area 242 of the eye sensed by one sensor. In Fig. 3C, the features corresponding to those described with respect to Fig. 3B are indicated by like numerals. In the event that the eye 260 only moves horizontally, the  $x$ -axis motion is the only motion that is detected. Accordingly, only one data input that tracks  $x$ -axis motion is required, and the area 242 aligned along the centerline 268 of the limbus 266 is sufficient. A procedure useful in constraining the motion of the eye 260 to the horizontal direction is described next.

[000117] Fig. 3D shows a diagram 206 that depicts a test pattern 282 and a fixation signal 290 that is useful for fixating an eye 260 of a person being tested when one sensor is employed in the eye monitoring device 120. The CRT 230 of Fig. 3A provides a frame 280 of visually displayed information. A test pattern 282 is disposed within frame 280, comprising one or more vertical lines 284 that can be traversed horizontally over a background 286. The eye 260 of the person being tested will in general attempt to follow the motion of the one or more lines 284. However, there in general can be a wandering of the gaze of the eye 260 in an upward or downward direction while the eye 260 attempts to follow the horizontal motion of the lines 284. The fixation signal 290, which is a prominent solid

line segment disposed horizontally across the test pattern 282, within a field of view of substantially 5 degrees total angular height or less, is provided to prompt the eye 260 to fixate vertically along the horizontal line 290 while not interfering with the proclivity of the eye 260 to follow the horizontal motion of the one or more vertical lines 284.

[000118] Fig. 4 is a flow chart 400 showing the steps in the operation of the instrument and method of the invention, or alternatively, showing the interrelationships among the modules comprising apparatus according to the invention. The description will be presented in terms of modules, but those of ordinary skill will also understand the figure as describing the steps of performing the method of the invention. Information is collected by imager 410 and data set collector 420 as necessary. In one embodiment, the information is a plurality of images. In another embodiment, the information is a plurality of data sets. In yet another embodiment, the information comprises at least one image and at least one data set. The information is transferred to the data analysis module 430 for analysis. A memory module 470 in bi-directional communication with the data analysis module 430 can record information sent from the data analysis module 430 in raw form, in analyzed form, or in both forms. Furthermore, the memory module 470 can store information, including as an archival storage, and can provide stored information to the data analysis module 430 as required. For example, the memory module 470 can provide information that was recorded during a previous visit of a patient to a medical practitioner for the purpose of comparing current information observed from the patient with historical information. Archived information can be stored locally or at a remote location. A remote storage capability, which is not shown, can be connected to memory module 470 and or to data analysis module 430 by any convenient means, including wire connection, wireless connection, and by the physical

movement of storage media, such as floppy disks, CD-ROM disks, DVD disks, magnetic tape, memory cards, and similar moveable storage media.

[000119] A superposition module 440 is in bi-direction communication with the data analysis module 430. Information can be sent from the data analysis module 430 to the superposition module 440, and data that has been subjected to superposition can be sent from the superposition module 440 to the data analysis module 430. As described below with respect to Fig. 5, the superposition module 440 in some embodiments comprises a plurality of other modules.

[000120] The data analysis module 430 is in communication with a data output module 450, which can provide information to a user. The data analysis module 430 is optionally in communication with a report module 460, which can provide reports to a user. The data analysis module 430 is optionally in communication with a display module 480 that can display images, sets of data, and superpositions of information to a user for visual examination of the information.

[000121] Fig. 5 is a diagram 500 depicting components of a superposition module 440 according to the invention. The superposition module 440 can optionally comprise first and second identification modules 510, 520 that identify first and second fiduciary points in an image or a data set. In some embodiments, the first and second identification modules 510, 520 are the same module. The superposition module 440 also optionally comprises an orientation module 530, a scaling module 540, and a correspondence module 550. The orientation module 530 orients images or data sets to be superimposed about a fiduciary point so that a first metric and a second metric are oriented in selected orientations. The scaling module 540 scales an image or data set so that a first unit of measure associated with the first

metric and a second unit of measure associated with the second metric in each image or data set to be superimposed are substantially equal to selected first and second values. The correspondence module 550 creates a one-to-one correspondence between the fiduciary point, the first metric and the second metric in a first image or data set to be superimposed with the fiduciary point, the first metric and the second metric in a second image or data set to be superimposed.

[000122] In some embodiments, the first metric and the second metric are first and second axial directions. In one embodiment, the first and second axial directions are coplanar but not parallel axial directions, such as two axes, for example the x and y axes in a Cartesian coordinate system. Other coordinate systems can be used equally well. In such an embodiment, the first unit of measure associated with the first metric is a length along the first axial direction, such as a number of units along an x-direction, and the second unit of measure associated with the second metric is a length along the second axial direction., such as a number of units along a y-direction. In other embodiments, the first metric is a first axial direction, the second metric is an angular displacement from the first axial direction, the first unit of measure associated with the first metric is a length along the first axial direction, and the second unit of measure associated with the second metric is a unit of angular measure. For example, the first metric is a heading or compass direction that is considered to be zero degrees relative to an origin (i.e., due North on a map), and the first unit of measure is a geometric distance along the heading (i.e., a radius of a circular arc), the second metric is an angle (i.e.,  $\theta$  degrees clockwise rotation), and the second unit of measure is an angular value, such as  $\theta = 90$  degrees. When a plurality of images, a plurality of data sets, or at least one image and at least one data set are scaled, rotated and/or translated such that corresponding



first and second metrics are made to coincide, the plurality of images, the plurality of data sets, or the at least one image and at least one data set will be capable of being superimposed.

[000123] In the display of such images, one can present the images side by side, or in superimposed configuration, one upon the other. The images can be compared by simple superposition, to show interrelationship of one or more features that appear in each. Alternatively, by superimposing one image on the “negative” of another, it is possible to make the difference (or the change between a first image and a second image) readily apparent. For example, a new feature appearing in a later image will become the only feature (or a highlighted image) displayed in a display comprising a “negative” of a first image superimposed upon (or summed with) a second, later, image. Images can be displayed in false color as well, so that regions of data sets that comprise substantially similar values can be readily discerned. For example, an image in which a first color is used to represent data points below a threshold value and a second color is used to represent data points exceeding the threshold value provides a display for a viewer in which the regions having specified ranges of values are readily identified. As required, more than two ranges can be assigned, and corresponding different colors can be used in the display of the data set.

[000124] Fig. 6 is a diagram 600 showing a region of frequency space having both temporal and spatial frequency variations, and indicating a typical person’s reaction thereto, as is known in the prior art. Fig. 6 is based on observations made by D.H. Kelly, which results were reported some years ago. In Fig. 6, the horizontal axis 610 is a logarithmic axis that represents the temporal frequency in cycles per second (cps) ranging from close to zero to approximately 100 cps. In Fig. 6, the vertical axis 620 is a logarithmic axis that represents

the spatial frequency in cycles per degree (cpd) ranging from close to zero to approximately 20 cpd. In this circumstance, degrees are measured as angular measure on the retina of an eye. As can be seen, there is a region 630 extending from about 7 cps to about 60 cps and from about 0.1 cpd to about 2 cpd, which region 630 is labeled "Spatial Frequency Doubling." The region 630 further includes a point indicated by the cross 635 that is in some embodiments a target spatial and temporal frequency operating point in the vicinity of 25 cps and 0.3 cpd. Within the Spatial Frequency Doubling region 630, a person with normal vision see a pattern that appears to be doubled in spatial frequency from its actual spatial frequency. Persons with compromised vision, or with other neurological difficulties, have difficulty perceiving the doubled spatial frequency pattern, or see it only at higher contrast.

[000125] Figs. 7A and 7B are drawings that depict a display space 710 that is segmented and includes an illustrative contrast pattern 720. In Figs. 7A and 7B, one segment 715 includes a high contrast pattern 720 and one segment 715 includes a lower contrast pattern 720', respectively. Each of Figs. 7A and 7B include a central region 730 that can in some embodiments be used to locate a fixation element, or a different contrast pattern than the patterns shown in segment 715. As may be understood from comparison of Figs. 7A and 7B, the more strongly contrasting pattern 720 of Fig. 7A can be transformed into the low contrast pattern of Fig. 7B by decreasing the dynamic excursion (or dynamic range) of the signal comprising high contrast pattern 720. High contrast pattern 720 is generated by providing a sinusoidally varying signal having bright and dim extremes, or strongly illuminated regions and weakly illuminated regions. It is expected that those with compromised neurological condition will perceive the contrast signal to disappear at a higher contrast level threshold than those with normal vision and normal neurological conditions.

Dyslexia may be indicated by an inappropriate response to contrast sensitivity tests, because in dyslexia the eye and the brain collaboratively misinterpret the spatial relationships in data.

[000126] Figs. 8 A, 8B and 8C are diagrams that show the relationship between an image and a data set, two images taken at different times, and a series of images, false color data representations, and data sets, respectively. As depicted in Figs. 8A, 8B and 8C, the interrelated images and data sets are displayed side-by-side. It will be understood, perhaps most readily by considering the two images of Fig. 8B, that two or more pieces of information can also be superimposed. Careful comparison of the leftmost image of Fig. 8A with either of the images of Fig. 8B will show that the leftmost image of Fig. 8A is larger in size than either image of Fig. 8B. As is seen in the images of Fig. 8B, many features of one image are also present in the other image, and the two images could easily be presented as either the superposition of one on the other, or the superposition of one over the negative image of the other, thereby highlighting the differences between the two images. In one embodiment, viewing the information in side-by-side presentation makes it easier to compare information, and may allow certain forms of analysis, but requires the viewer to synthesize the data to find certain correspondences. In other embodiments that use superposition, benefits that accrue include the ability to highlight, the ability to subtract or otherwise process information, and the ability to assure that two pieces of information are representative of the same area or feature.

[000127] In Fig. 8A, the left image is an image 805 of a retina of an eye, including a macula 810 near the center of the image. In Fig. 8A, the right image 808 is a map of a contrast level observation, in which the central region 730 corresponds to the macula 810, and the region 715 having the contrast pattern 720 therein is intended to convey the

information that the observed response of the eye was acceptable in that region 715.

[000128] In Fig. 8B, the left image 805' is a first image of a retina of an eye, in which the macula 810 is again visible. The right image is an image that represents a second image of the same retina taken 6 months later, in which the macula 810 is again visible. However, in the later right image 805'', a new feature 820 appears to the left of the macula 810. The side-by-side presentation in Fig 8B is intended to show that for highly similar images, it is relatively easy to compare two or more images, as can be seen in a comparison of the two images in Fig. 8B, wherein a large number of features can be observed to be substantially common to both images, such as the position and shape of imaged blood vessels 830. While the new feature 820 is readily apparent, it is not clear from the image whether the new feature 820 represents an active proliferation of capillaries (i.e., blood is still circulating in blood vessels) or whether the new feature is a blood clot that has long since ceased to circulate. More information is available from a consideration of the images shown in Fig. 8C.

[000129] Fig. 8C comprises four pieces of information. The leftmost image is the image 805'' as seen in Fig. 8B, right side. This is a high resolution image that is displayed on a pixel by pixel basis, wherein much detail is available for analysis. Again, the feature 820 is visible. The next panel in Fig. 8C (i.e., the second image from the left) is a false color oxygen saturation view 820A of the region of the retina in the vicinity of the new feature 820. In the second image 820A, one can discern that the new feature 820 is a region centered on a junction 825 of blood vessels 830, which gives further credence to the analysis that the feature 820 represents blood high in oxygen. The next image 806 (i.e., the third image from the left) is a false color thermal image taken at lower resolution than the second image from the left (i.e., 4 by 4 pixels rather than one-by one pixel), which image shows the new feature

820, for example, as a red (false color) square region 820' at the junction 825 of a yellow (false color) blood vessels 830. The red false color is representative of a higher temperature than the immediate surroundings, suggesting that the new feature 820 is a proliferation of capillaries that comprises fresh, warm blood, rather than an old bleed which would have reached the same background temperature as the surrounding tissue, and therefore would have been represented by the same color (green). A second red false color region 832 is also shown in the false color image, the second red false color region corresponding to the macula 830, which is rich in blood vessels, and therefore would be expected to be somewhat warmer than the surrounding area. The rightmost panel of Fig. 8C is a representation 809 of a data set obtained from a contrast sensitivity measurement, in which the central region 812 corresponds to the macula 810 of the leftmost image 805''. The data set is represented at a rather low resolution as compared to the leftmost image 805'', for example using a 10 pixel by 10 pixel resolution. The gray region 850 of the contrast sensitivity data set represents a region of severely degraded response, which corresponds to the location of the new feature 820 in the leftmost panel of Fig. 8C. One can then recognize from the aggregation or interrelation of images 805'', 820A, 806, and 809, that the new feature 820 gives all the indications of a region representing an active capillary structure, the structure negatively impacting the vision of the eye under consideration.

[000130] Fig. 9 is an illustrative schematic in exploded form showing the relationship among superimposed images and/or data sets. In Fig. 9 there are three parallel planes 910, 920 and 930. Situated on each plane is an image or a map of a data set. For example, there appears on plane 910 image 912 that is a photographic image of the fundus of an eye such as is captured by a retinal camera 134. Along axis A, which is denoted by a dotted line

extending between the planes 910, 920, 930, there is in image 912 a spot 914, which corresponds to the area of capillaries described as the new feature 820 of Figs. 8B-8C. Along axis B, which is also denoted by a dotted line extending between the planes 910, 920, 930, there is in image 912 a macula 916, which corresponds to the macula of Figs. 8A-8C. There are blood vessels 913 that have a junction 915, as well as other features visible in image 912.

[000131] In plane 920 of Fig. 9 there appears an image that is a false color thermal image taken at a lower resolution than the second image from the left (e.g., 4 by 4 pixels rather than one-by one pixel), which image shows the new feature 820 as a red (false color) rectangular region 924 at the junction 925 of yellow (false color) blood vessels 923. The A axis passes through the rectangular region 924 representing the false color image of the new feature 820. The B axis passes through the square false color region 926 corresponding to the macula 916 of the eye.

[000132] In plane 930 of Fig. 9 there appears a map 932 corresponding to a data set recorded as a result of a contrast sensitivity test. In the map 932 there is a fixation pattern 936 which is the area upon which the gaze of the eye under test is expected to fall, and as described above, is a location where the gaze of the eye can be observed to fall by instrumentation of the invention. Accordingly, the fixation pattern 936, or a selected pixel of the fixation pattern 936, such as the center of the fixation pattern 936, can be placed along Axis B so as to coincide with (or to be superimposed upon) the image of the macula 916 and the false color image 926 of the macula. Also, the region 934 of the map 932 corresponding to the data set obtained in the contrast sensitivity test indicates a diminution in the ability of the eye to perceive the contrast pattern, which diminution is denoted by a gray hue in area 934. In some embodiments, the depth or intensity of the gray hue, or the use of a range of

false colors, can be used to represent the severity of the diminution of perception. The region 934 is aligned with Axis A, corresponding to the area of the retina having the new feature 820 that is depicted as region 914 of the fundus photograph 912. As needed, the sizes of one or more of the various images and maps or other representations of data sets can be expanded or contracted so that superposition is possible. Furthermore, any of the images or representations of data sets can be translated and/or rotated to orient one with respect to another so that superposition can be accomplished. As is understood in the geometric arts, superposition can be attained by superimposing two selected points in a first image with the corresponding two selected points in a second image. Superposition can also be attained by defining a pair of coplanar but not parallel vectors in each image, causing the dimensions of the images to be commensurate by expanding or contracting at least one image as needed, and aligning the vectors. Superposition can also be accomplished by defining an origin and a vector in each image, causing the dimensions of the images to be commensurate by expanding or contracting at least one image as needed, and aligning the origins and the vectors.

[000133] According to principles of the invention, it is possible to determine blood glucose by measuring the eye of a patient using an instrument as shown in Fig. 10, and described in more detail below.

[000134] The operation of the instrument is based on the observation that in humans, and perhaps in other animals, the retina of the eye has one of the fastest metabolic rates in the body. Diabetes is a disease that is characterized by poor control of blood glucose. Diabetics attempt to control their blood glucose levels by balancing food intake, exercise and medication, such as insulin or other medications. In order to determine whether and how

much insulin to administer, the blood glucose level of the individual must be measured.

Today, diabetics can be required to draw blood, commonly by pricking a finger, several times a day. The procedure of drawing blood can be painful and invasive, and compliance with a strict medical regimen may be affected in a negative way.

[000135] The blood glucose determination apparatus of the invention, and its method of use, may have applicability in blood glucose monitoring in diabetics, with several advantages. First, the measurement does not require the drawing of blood, and is therefore painless. In addition, the measurement device will not require the use of consumables, such as chemicals or treated strips that interact with drawn bodily fluids. The lack of consumables, other than a replaceable battery, will reduce the operating cost per test, making testing possible at lower operating costs than in conventional tests that require interaction of a bodily fluid with a test medium. In addition, the absence of consumables will make testing more convenient in that the user does not need to remember to transport consumable items when he or she travels from home, even during the day. Another benefit is the fact that the test will be relatively unobtrusive and not embarrassing, so that it can be performed quickly and in public settings as may be required.

[000136] Experimenters have studied the effects of glucose on the retina, the heart, and the kidneys for many years. These organs are well-known to be negatively affected in persons suffering from diabetes. One relation that has been noted is the ability of the retina to observe or determine contrast, which varies with the blood glucose level. In particular, a relation between a person's visual contrast sensitivity and the person's blood glucose level may provide a basis for measuring the blood glucose level. It may be necessary or advantageous to calibrate the measurement by the use of a blood glucose measurement using



drawn blood. However, once the calibration is performed, the necessity to draw blood to make actual measurements is obviated. The calibration might also be performed by using different blood glucose levels, e.g., high blood glucose, normal blood glucose, and low blood glucose, which levels may be induced by deliberate administration of foodstuffs or by the deliberate withholding of food and having the person to be tested perform exercise.

[000137] The apparatus 1000 of Fig. 10 is in one embodiment a hand-held device that measures a person's visual contrast sensitivity in the same way that the FDT device measures contrast sensitivity in persons exhibiting glaucoma and/or other neurological disorders. As shown in Fig. 10, the apparatus 1000 comprises a power supply 1010 such as a battery and electronics 1020 for generating and displaying a contrast pattern 1030 that appears on a display 1040 and for computing a result of a blood glucose measurement. In one embodiment, the electronics 1020 comprises a microprocessor or microcontroller and memory, as well as the necessary signal acquisition and conditioning hardware for responding to commands from the user, as well as software that may be recorded in nonvolatile form in a machine-readable medium. In one embodiment, the display 1040 will be an LCD similar to those used in present-day camcorders. In other embodiments, other display technology may be used. The apparatus 1000 also comprises a lens 1050 for focusing an image of the contrast pattern 1030 so that the image may be viewed by an eye 1070 of a user. The contrast pattern 1030 can also include a fixation element 1032, for assisting the user in fixing his or her gaze on a particular location of the display. The apparatus 1000 also can comprise an optical element 1060 useful for changing a size of the image and/or for causing the light from the image to be correctly oriented for the user to view the image. In some embodiments, the optical element 1060 is a mirror, which can be a planar mirror, a

convex mirror, or a concave mirror as required. The eye 1070 as shown comprises an iris 1072 and a lens 1074, as is commonly found in eyes for causing an image to fall on a retina 1076 of the eye.

[000138] In use, the user holds the apparatus 1000 in a position such that the user can observe the contrast pattern 1030 and the fixation element 1032. The fixation element 1032 help to insure that the contrast pattern 1030 will fall on the same portion of the user's eye 1070, such that the same area of the retina 1076 of the eye 1070 is interrogated. The area can be any area of the retina that represents the test subject's reaction to blood glucose level or concentration. In some embodiments, the area is the macula of the eye 1070, in which case the contrast pattern 1030 and the fixation element 1032 are coincident. For example, the contrast pattern 1030 can be centered on the fixation element 1032. In one embodiment, the user can activate a button 1080 on the apparatus 1000 during a time when he or she can see the contrast pattern 1030. The button 1080 is connected electrically to the electronics 1020. In one embodiment, the user releases the button 1080 to indicate that the user can no longer distinguish the contrast sensitivity pattern 1030, thereby completing a test cycle. The contrast sensitivity pattern 1030 first appears with dark lines and light lines, which respectively become lighter and darker with time. At some point, either when the two sets of lines in the contrast sensitivity pattern 1030 have the same optical characteristic and cease to be distinguishable, or when the user is no longer able to distinguish between the light and dark sets of lines, the user would be expected to release the button 1080. After the electronics 1020 processes the data it receives, and computes a blood glucose level for the user, the result may in some embodiments be displayed to the user by being presented on the display 1040 of the apparatus 1000 in any of an alphanumeric format, a pictorial format (i.e., a graphic or an

icon), an audible signal provided by a speaker 1082, a tactile signal provided by a vibrator, or any combination of signals. In alternative embodiments, the result can be transferred, for example by wireless communication, to another device, such as a personal digital assistant, a cellular telephone, a computer, a data recorder, a printer, or an external display. For example, a person may wish to have a result that indicates a serious abnormality, such as severe hypoglycemia, reported to another trusted party to make sure that appropriate medical intervention takes place.

[000139] Those of ordinary skill will recognize that many functions of electrical and electronic apparatus can be implemented in hardware (for example, hard-wired logic), in software (for example, logic encoded in a program operating on a general purpose processor), and in firmware (for example, logic encoded in a non-volatile memory that is invoked for operation on a processor as required). The present invention contemplates the substitution of one implementation of hardware, firmware and software for another implementation of the equivalent functionality using a different one of hardware, firmware and software. To the extent that an implementation can be represented mathematically by a transfer function, that is, a specified response is generated at an output terminal for a specific excitation applied to an input terminal of a “black box” exhibiting the transfer function, any implementation of the transfer function, including any combination of hardware, firmware and software implementations of portions or segments of the transfer function, is contemplated herein.

[000140] While the present invention has been explained with reference to the structure disclosed herein, it is not confined to the details set forth and this invention is intended to cover any modifications and changes as may come within the scope of the following claims.